REMARKS

I. TRAVERSAL OF RESTRICTION

In an action mailed May 3, 2005, the Examiner restricted pending claims 102-131 via three criteria into an unstated and unclear number of additional restriction groups. Specifically, the Applicants were required to elect: (1) an assay milieu, (2) a particular polypeptide and (3) a particular secretase substrate peptide. The Applicants respectfully traverse.

Assay "Milieu"

The Examiner stated that claims 102-128 and 131 are drawn to *in vitro* competitive binding assays and claims 129 and 130 are drawn to *in vivo* competitive binding assays. According to the Examiner, these groups of methods lack "unity of invention" because these inventions fail to share a special common technical feature. The MPEP defines "special common technical features" as those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art." (See MPEP § 1850; pg. 1800-95).

With respect to the current claim set, one technical feature that makes a contribution over the prior art is a novel substrate for the β-secretase polypeptide which is useful to assay for modulators of β-secretase activity. All the claims recite a novel substrate or novel genus of substrates that have not been used in a beta secretase assay in the cited art. For example, claims recite a substrate comprising the elected peptide SYEV, or a genus comprising this substrate.

To support the lack of unity allegation, the Examiner alleged that the following are known in the art: a polypeptide with β-secretase APP processing activity, substrate thereof of (EVNL-DAEFR), use of these in an assay, and secretase substrates comprising P2P1-P1'P2' motif of KMDA. These allegations do not support a conclusion of "lack of unity" because the claims presented by the applicants *exclude* embodiments consisting of these features. Notably, the claims specifically state that the peptides encompassed by the claims do not comprise the corresponding P2P1-P1'P2" portion of SEQ ID NO: 20 (KMDA). Thus, even if "lack of unity" were a valid basis to restrict this

application or this claim set (and it is not), the Examiner has not established a valid unity objection by identifying a lack of a "special" common technical feature of the claims. The use of the substrates recited in the claims with a beta secretase enzyme is a unifying feature, irrespective of the "milieu."

The Applicants also dispute the "in vitro/in vivo" interpretation given to the current claim set, with the exception of claim 130, which requires the assay be carried out in a live non-human animal.

The Examiner also alleged that the two alleged "milieu" would require separate and burdensome searches because they involve divergent subject matter. No reasoning was provided in support of this allegation, and it is untrue. The searching will involve an evaluation of art relating to assays to identify modulators of beta secretase activity irrespective of whether or not the claim specifies an "in vivo" limitation. The body of prior art is the same and there is merely additional limitations for which to search for select claims, which amounts to nothing more than the usual and customary burden of any dependent claims.

Polypeptides with β-Secretase Activity

The Examiner also required election of a single β-secretase polypeptide (SEQ ID NO: 2 or SEQ ID NO: 4) and identification of claims readable thereon. One alleged basis for this restriction was the absence of "a substantial structural feature disclosed as being essential" to utility as a beta secretase. In actuality, SEQ ID NO: 2 and NO: 4 are identical except for a 25 amino acid insertion/deletion in one sequence relative to the other. In other words, the two sequences are putative splice variants that arise from the sequence, with 476 common amino acid residues which form various common functional domains (e.g., signal sequence, pro-peptide, DTG/DSG active site tri-peptide motifs, transmembrane domain, etc.).

The second alleged basis for requiring election was unduly burdensome searching. The Examiner has not explained what burden would exist in examining claims to both β-secretase polypeptides. In fact, no such burden exists. For example, the numerous Gurney et al. beta secretase patents that have already issued to the assignee of this application disclose both the long and short form splice variants of human beta secretase, as well as murine beta secretase, in a single document. (See, e.g., any of Gurney et al., U.S. Patent Nos.

6,699,671; 6,828,117; 6,825,023; 6,737,510; 6,797,487; 6,753,163; 6,867,018; 6,844,148; 6,835,565; 6,790,610; 6,727,074; 6,706,485; 6,500,667; 6,440,698; and 6,420,534.)

Taking Patent No. 6,844,148 as an example, not only does the specification describe the human long and short form of beta secretase, murine form, and active variants thereof, but the claims are directed to secretase assays that involve use of SEQ ID NO: 2, variants thereof (e.g., 95% identity, transmembrane deletion fragments, N-terminal and C-terminal deletion fragments, cell-free and cell-based assays, and use of multiple substrates. This is direct evidence that neither search nor examination require undue burden.

Because SEQ ID NOS: 2 and 4 are related sequences wherein SEQ ID NO: 4 has a deletion of 25 amino acids at residue 190, relative to SEQ ID NO: 2, but the sequences otherwise comprise long stretches of identical sequence, any computerized sequence-based search will uncover all art related to either sequence. For this reason too, a search based on both β-secretase polypeptides is not unduly burdensome, and the election requirement should be withdrawn.

Secretase Substrate

The Examiner alleged that the scope of the peptides that comprise the elected peptide (SYEV) is large since there is no limit placed on the number of amino acids of the peptide. Therefore to search the entire scope would be unduly burdensome. The Examiner required the Applicants to elect a single peptide that comprises SYEV. Applicants traverse this restriction of substrate species because (1) it is inconsistent with the Petition Decision dated October 27, 2004; (2) Applicants election on January 27, 2005 was consistent with the Petition Decision; and (3) the Examiner is using the restriction requirement to limit the claimed polypeptide and this is not the appropriate venue to limit the size of the peptide. Moreover, examination would not be unduly burdensome, especially in the context of the elected method claims.

At pages 9-10 of the Petition Decision, Director Kisliuk required that Applicants elect a peptide from one of Groups 1-2940 drawn to a peptide P2-P1-P1'-P2' wherein P2, P1, P1' and P2' are each selected from the amino acid residues set out in the Table 1. Thus, the Group Director has already divided peptide subject matter of the invention into almost *three thousand* groups, greatly easing the PTO burden to the detriment of the

Applicants. In the response to this decision, mailed January 27, 2005, Applicants elected one peptide from Table 1: SYEV. Further, Applicants pointed out the claims which encompass this peptide. Thus, the election of peptide SYEV is proper, and an additional restriction requirement is not the appropriate method for an Examiner to limit the size of the claimed peptide.

The Examiner did not acknowledge the presence of the linking claims and attempts to limit the generic limiting claim to an elected invention. Director Kisliuk states at page 11 of the Decision " Applicants are correct that they deserve examination of the generic linking claim along with the elected invention." Generic claims 102-131 encompass (use of) the elected species SYEV and according to the MPEP and the petition decision the Examiner should examine these claims. The petition process to correct the first improper restriction interrupted substantive examination for a year, and it would be grossly unfair to ignore the Group Director's decision at this stage and, in essence, further restrict the nearly three thousand peptide groups by peptide length.

Moreover, the burden of examination is substantially less in the context of method claims elected by the Applicants. Even if the computer-based sequence search based on the substrate peptide sequence identifies a large initial pool of literature, the pool can be expected to be easily reduced (or completely eliminated) in the context of additional limitations of the elected method claims. In the absence of a teaching or suggestion in the prior art to use a peptide as a beta secretase substrate as recited in the method claims, the claims will be novel and unobvious. The ability to limit the peptide search with other search parameters greatly lessens the burden perceived by the Examiner.

II. ELECTION

Applicants hereby elect (1) an in vitro (Group I) assay milieu; (2) a β-secretase polypeptide having the amino acid sequence of SEQ ID NO: 2 (or active fragments of this prepro-enzyme); and (3) a substrate having the amino acid sequence SEISY-EVEFR.

With respect to election (2), claims 102-131 all read on the elected embodiment. With respect to election (3), at least claims 102-111, 117, 119-122, and 124-131 are believed to read on the elected species.

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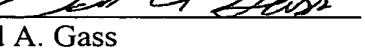
Respectfully submitted,

By 

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